REMARKS

Claims 1-85, 89-95, 102-108, 115-117, 122-132, 134-137, 140-146, 148-150, 153-159, 161-163 and 166-169 are pending.

The Claimed Compounds are Not *prima facie* Obvious in View of the Cited Patents.

Reconsideration is requested of the rejection of claims 1-85, 89-95, 102-108, 115-117, 122-132, 134-137, 140-146, 148-150, 153-159, 161-163 and 166-169 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of Holton et al. (U.S. Patent No. 6,462,208) and claim 1 of Holton (U.S. Patent No. 6,610,860).

It is respectfully submitted that the subject matter of the claims of the present application would not have been obvious in view of the claims of the cited patents. The invention as a whole must be considered and compared to the prior art teaching. The Office cannot focus on one position of the tetracyclic taxane and compare only that position to the prior art teaching. The pending claims are directed to compounds comprising a combination of substituents at multiple positions of the depicted molecular structure. *Prima facie* obviousness of a claim to such combinations is not established by the mere fact that the compounds covered thereby form a subset of the compounds covered by the claims of the reference patent. Absent an identified motivation or suggestion in the art for making the selection, there can seldom be a realistic basis for *prima facie* obviousness where, as here, the selection of substituents at each of several different positions is either narrower than, or entirely differs from, the generic definitions reflected in the claims of the reference.[1] To support a rejection for obviousness, there must be evidence in the record establishing a motivation to make the selection, in this case the multiple selections, that are required to arrive at the combination called for by the pending claims.[2] Such evidence may come from the references, the skill in the art,

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[1]In re Baird, 16 F.3d 380, U.S.P.Q.2d 1550 (Fed. Cir. 1994).

[2]In re Sang-Su Lee, 277 F.3d 1338, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002).

or the nature of the problem.[3] In the instant action, the Office has failed to make any showing of a motivation or suggestion to select the compounds of the amended claims in view of the compounds claimed in the cited patents, and has thus failed to establish a *prima facie* case of obviousness for the amended claims in view of the claims of the cited patents.

When evaluating the scope of a claim, every element of the claim must be considered.[4] Thus, while the Office has chosen to focus on the C7 and 3'N groups of the claimed compounds,[5] the entire compound, with all of its elements, must be examined and compared to the reference claims as a whole. To support a conclusion of obviousness, there must be evidence of a motivation or suggestion to modify the combination of multiple substituents as described in the reference claims to yield the multiply different combination of substituents defined in the instant claims. Here the record is devoid of any evidence of any such motivation or suggestion. Thus, the Office has failed to establish a *prima facie* case of obviousness-type double patenting with respect to the claimed compounds.

In evaluating statutory obviousness, the claimed subject matter as a whole must be compared to the prior art as a whole. Analogously, in evaluating obviousness type double patenting, the obviousness of each claim at issue must be compared to the claims of the reference patent as a whole. *Prima facie* obviousness cannot be found absent evidence that one skilled in the art would have been led to select the specifically claimed combination of features from the overall claim structure of the reference, including disclosure in the reference claims that may teach away from the combination defined in the claims under examination. It is respectfully submitted that the instant Office action contains no such showing. Nor has the Office identified any motivation in

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[3]Brown & Williamson v. Philip Morris, 229 F.3d 1120, 56 U.S.P.Q. 2d 1456 (Fed. Cir. 2000), Ruiz v. A.B. Chance, 350 F.3d 1270 (Fed. Cir. 2004).

[4]See, e.g., In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995).

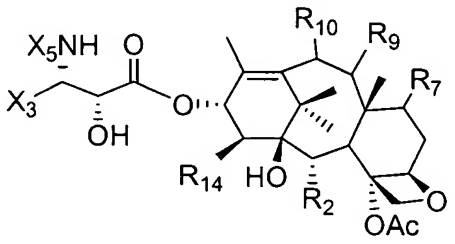
[5]See Office action dated July 28, 2004, p.2.

the level of skill in the art, or in the nature of the problem, that would afford impetus for the requisite modifications.

Only by liberal application of hindsight could one skilled in the art arrive at the multiple selections necessary to arrive at the instantly claimed scope of compounds from the teachings that may be found in the claims of the reference patents. It is respectfully submitted that the Office action proceeds in just such fashion. With knowledge of the claimed structure, the text of the action identifies the selections that must be made to yield the claimed combination. But, hindsight reconstruction of the applicant's claims from the prior art is impermissible. The Office cannot use applicant's invention as a template to determine the claims are obvious in view of the prior art, i.e. by hindsight. The motivation to modify the compounds of the prior art must be gleaned by a person of ordinary skill from the prior art. As stated above, U.S. Patent No. 6,462,208 does not provide a motivation to modify the compounds of that patent to arrive at the claimed compounds.

1. U.S. Patent No. 6,462,208

Subject claim 1 is directed to a C7 ester substituted taxane having the following structure:



wherein

R_2 is acyloxy;

R_7 is $R_{7a}COO$-;

R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon atom of which R_{7a} is a substituent and wherein said

substituted hydrocarbyl is substituted with a group selected from halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, acyloxy, nitro, cyano, thiol, ketals, acetals and ethers;

R_9 is keto, hydroxy, or acyloxy;

R_{10} is hydroxy;

R_{14} is hydrido or hydroxy;

X_3 is heterocyclo;

X_5 is $-COX_{10}$, and X_{10} is alkyl, alkenyl, alkynyl or heterocyclo; or

X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, n-butyl, iso-butyl, sec-butyl, cyclobutyl, n-pentyl, iso-pentyl, tert-pentyl, sec-pentyl, cyclopentyl, n-hexyl, iso-hexyl, sec-hexyl, tert-hexyl, cyclohexyl, alkenyl, alkynyl or heterocyclo; and

Ac is acetyl.

In and effort to elucidate the analysis, applicant has grouped the claims with respect to the C7 substituent. For example, Group I includes claims 1, 122-125, 140-142 and 153-155. Claim 1 is representative of Group I and is directed to tetracyclic taxanes including an ester moiety at the C7 position (R_7). Group II includes claims 2-29, which are dependent on claim 1, incorporate all the limitations of claim 1 and further define the C7 substituent as $-OC(O)R_{7a}$ wherein R_{7a} is C_2-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl. Group III includes claims 30-57, 126-129, 143-145 and 156-159 which further define R_{7a} as C_2-C_8 alkyl. Group IV includes claims 58-85, 130-132, 135-137, 146, 148-150, 159 and 161-163 which further define R_{7a} as ethyl. Group V includes claims 89-95 and 166-169 directed to tetracyclic taxanes including an ester moiety at the C7 position. Finally, Group VI includes claims 102-108 and 115-117, which further define R_{7a} as ethyl or propyl.

The claims of each group are separately and independently patentable over the '208 patent because the selection of the combination of the many substituents of the tetracyclic taxane in combination with the definition of R_{7a} for each different claim group is not suggested by nor is it obvious from the claims of the '208 patent.

A. Group I (Claims 1, 122-125, 140-142 and 153-155)

Claim 1 is representative of the Group I claims of the present application and is described in detail above. The following Table 1 details the substituents of the tetracyclic taxane for subject claim 1 and compares them to the substituents cited in claims 8 and 9 of the '208 patent.

Table 1.

Substituent Position	Subject Claim 1	Claims 8 and 9 of '208
C1	β-OH	hydrogen, hydroxy, protected hydroxy, or together with R_{14} forms a carbonate
C4 and C5	β-oriented oxetane ring with an α-acetoxy substituent attached to C4	oxetane ring with an acetoxy substituent attached to C4
C7	$R_{7a}COO$- (R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon atom of which R_{7a} is a substituent)	acyloxy
C9	keto (oxo), hydroxy or acyloxy	oxo
C10	hydroxy	hydroxy
C19	β-methyl	methyl
C2'	α-OH	-OX_6 (wherein X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or functional group which increases the water solubility of the taxane derivative)

C3'N	$-COX_{10}$ (wherein X_{10} is alkyl, alkenyl, alkynyl or heterocyclo) or X_5 is $-COOX_{10}$ (wherein X_{10} is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, n-butyl, iso-butyl, sec-butyl, cyclobutyl, n-pentyl, iso-pentyl, tert-pentyl, sec-pentyl, cyclopentyl, n-hexyl, iso-hexyl, sec-hexyl, tert-hexyl, cyclohexyl, alkenyl, alkynyl or heterocyclo)	t-butoxycarbonyl
C3'	heterocyclo	furyl or thienyl

Notably, with respect to the nitrogen substitution, the compounds of claims 8 and 9 of the '208 patent and the compounds of the subject claims (particularly claims 1 and 89) are mutually exclusive (X_5 for the subject claims excludes t-butoxycarbonyl). Moreover, not only does U.S. Patent No. 6,462,208 fail to provide motivation for modifying the compounds disclosed to arrive at the combination of the numerous taxane substituents defined in subject claim 1, but the '208 patent effectively teaches away from the compounds defined by claim 1.

As illustrated in the table, subject claim 1 defines compounds wherein the combination of substituent selections is different at multiple designated positions of the tetracyclic taxane structure from the compounds defined by claims 8 and 9 of the '208 patent. For example, at the C1 and C2' positions, subject claim 1 defines stereochemistry as well as a subset of the possible substituents defined in claims 8 and 9; and at the C4 and C5, and C19 positions, subject claim 1 defines stereochemistry, whereas claims 8 and 9 do not. Stated another way, the selection of specific substituents at certain positions of the taxane in claims 8 and 9 would not have led from the universe of compounds of the '208 patent to the compounds of claim 1 wherein a different combination of the multiple taxane substituents was selected.

Noting that the '208 patent may be considered a § 102(b) reference, applicant further directs the Examiner's attention to the failure of the '208 specification to have led

a person of ordinary skill to select the compounds defined by subject claim 1. Subject claim 1 is described above and excludes compounds having an acetoxy substituent at the C7 position and a t-butoxycarbonyl group at the C3'N position. In contrast, Examples 1 and 2 of the specification disclose compounds having a C7 acetoxy group and a C3'N t-butoxycarbonyl group with a balance of substituents conforming to docetaxel. Furthermore, the specification teaches away from selection of the substitution pattern described by subject claim 1. The '208 patent exemplifies taxanes having a t-butoxycarbonyl group at the C3'N position, a hydroxy at the C10 position and an acetoxy at the C7 position, with the balance of substituents conforming to docetaxel, which are outside the group of taxanes defined by claim 1. Although the Office states that the C7 and 3'N substituents of claim 1 are obvious based on the analogous alkyl groups, the reference as a whole teaches away from selection of a C7 substituent other than acetoxy and a 3'N substituent other than t-butoxy carbonyl. Other compounds exemplified are farther removed from the scope of subject claim 1. Accordingly, the compounds exemplified in the '208 patent would have led a person of ordinary skill away from the compounds defined by subject claim 1. Thus, U.S. Patent No. 6,462,208 teaches away from the compounds defined by claim 1.

Claims 122-125 and 140-142 define pharmaceutical compositions of the compounds of claim 1 and are patentable for the same reasons as claim 1. Furthermore, claims 153-155 define methods for inhibiting tumor growth by oral administration of the compounds of claim 1 and are patentable for the same reasons as claim 1. Accordingly, the compounds of claim Group I are patentable in view of claims 8 and 9 of the '208 patent.

B. Group II (Claims 2-29)

The claims of Group II are dependent on claim 1 (Group I) and incorporate all the limitations of claim 1; accordingly, the arguments relating to the selection of the combination of the multiple taxane substituents apply equally to Group II. Additionally, claim 2 is representative of Group II and the C7 position is defined as $-OC(O)R_{7a}$ wherein R_{7a} is C_2-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl. The compounds of claims 8

and 9 of the '208 patent have an acyloxy group at the C7 position and neither claims 8 nor 9 (nor Examples 1 and 2) would have suggested the selection of an ester group substituted with C_2-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl group at the C7 position from the universe of acyloxy groups disclosed in the '208 patent. In addition, the claims and specification of the '208 patent as a whole teach away from the selection of compounds having the combination of various substituents defined in claim 2 and a C7 acyloxy group substituted with a C_2-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl group. The '208 patent would have led a skilled artisan to multiply different combinations of substituents and to a C7 substituent of either hydrogen or acetoxy. Thus, the compounds of claim Group II are patentable in view of the '208 patent.

C. Group III (Claims 30-57, 126-129, 143-145, 156-158)

The claims of Group III are dependent on claim 1; accordingly, the arguments relating to the selection of the combination of taxane substituents apply equally to Group III. Additionally, claim 30, which is representative of Group II, further define R_7 as -OC(O)R_{7a} wherein R_{7a} is C_2-C_8 alkyl. Although the compounds disclosed by the '208 patent have an acyloxy group at the C7 position, the multiply different combination of substituents at the other positions defined by claims 8 and 9 (and Examples 1 and 2) would not have suggested the selection of the combination of substituents at the multiple designated positions of the tetracyclic taxane and an ester group substituted with an C_2-C_8 alkyl group at the C7 position. Moreover, as described above the disclosure of the '208 patent would have taught away from such a combination as defined by claim 30. Furthermore, claims 126-129 and 143-145 define pharmaceutical compositions wherein the -OC(O)R_{7a} group defines R_{7a} as ethyl and propyl and claims 156-158 define methods for inhibiting tumor growth by oral administration of compounds wherein the -OC(O)R_{7a} group defines R_{7a} as ethyl and propyl. As there would have been no motivation to select the particular C7 ester groups of the compounds of Group III combined with the many other taxane substituents as described above, the compounds of claim Group III are patentable in view of the '208 patent.

D. Group IV (Claims 58-85, 130-132, 135-137, 146, 148-150, 159, 161-163)

The claims of Group IV are dependent on claim 1; accordingly, the arguments relating to the selection of the combination of many taxane substituents apply equally to Group IV. Additionally, claim 58, which is representative of Group IV, has a propionyloxy group at the C7 position. The compounds of the '208 patent have multiply different combinations of substituents for the multiple positions of the taxane and an acyloxy group at the C7 position; accordingly, claims 8 and 9 (and Examples 1 and 2) would not have suggested the selection of the combination of substituents at the multiple designated positions of the taxane with a propionyloxy group at the C7 position.

Additionally, claims 130-132, 135-137, 146 and 148-150 are directed to pharmaceutical compositions containing compounds having a propionyloxy group at the C7 position. Furthermore, claims 159 and 161-163 are directed to methods of inhibiting tumor growth by oral administration of a pharmaceutical composition containing a taxane having a propionyloxy group at the C7 position. Because the '208 patent would have failed to motivate selection of the multiply different combination of taxane substituents with a C7 propionyloxy group, the compounds of claim Group IV are patentable in view of the '208 patent.

E. Group V (Claims 89-95, 166-169)

Claim 89 is representative of the Group V claims of the present application. The following Table 2 details the substituents of the tetracyclic taxane for subject claim 89 and compares them to the substituents cited in claims 8 and 9 of the '208 patent.

Table 2.

Substituent Position	Subject Claim 89	Claims 8 and 9 of '208
C1	β-OH	hydrogen, hydroxy, protected hydroxy, or together with R_{14} forms a carbonate
C2	α-benzoyloxy	benzoyloxy
C4 and C5	β-oriented oxetane ring with an α-acetoxy substituent attached to C4	oxetane ring with an acetoxy substituent attached to C4
C7	$R_{7a}COO$- (R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon atom of which R_{7a} is a substituent)	acyloxy
C9	keto (oxo)	oxo
C10	hydroxy	hydroxy
C19	β-methyl	methyl
C2'	α-OH	-OX_6 (wherein X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or functional group which increases the water solubility of the taxane derivative)

C3'N	$-COX_{10}$ (wherein X_{10} is alkyl, alkenyl, alkynyl or heterocyclo) or X_5 is $-COOX_{10}$ (wherein X_{10} is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, n-butyl, iso-butyl, sec-butyl, cyclobutyl, n-pentyl, iso-pentyl, tert-pentyl, sec-pentyl, cyclopentyl, n-hexyl, iso-hexyl, sec-hexyl, tert-hexyl, cyclohexyl, alkenyl, alkynyl or heterocyclo)	t-butoxycarbonyl
C3'	heterocyclo	furyl or thienyl

Notably, as described in detail above for Group I, the compounds of claim 89 are mutually exclusive of the compounds defined in claims 8 and 9 of the '208 patent. Moreover, the selection of the multiply different combination of substituents defined by claim 89 would not have been suggested by the disclosure of the '208 patent. In actuality, as described for claim 1, the '208 patent teaches away from the selection of the combination of substituents required by claim 89. Thus, as above for claim 1, claim 89 is patentable in view of the '208 patent.

Claims 90-95 incorporate all the elements of claim 89 and further define substituents of the taxane compounds. Claims 166-167 are directed to methods of inhibiting tumor growth through oral administration of pharmaceutical compositions containing the taxane compounds of claim 89. Claims 168-169 are directed to pharmaceutical compositions of the compounds of claim 89. Thus, the claims of Group V are patentable over the '208 patent for the same reasons as claim 89.

F. Group VI (Claims 102-108, 115-117)

The claims of Group VI are dependent on claim 89; accordingly, the arguments relating to the selection of the combination of the many taxane substituents apply equally to Group VI. Claim 102 is representative of Group VI and further comprises a propionyloxy or butyryloxy group at the C7 position. The compounds defined by claim

102 have multiply different combinations of taxane substituents (as detailed in Table 2) and a propionyloxy or butyryloxy group at the C7 position; the compounds of the '208 patent have an acyloxy group at the C7 position. Claims 8 and 9 (and Examples 1 and 2) would not have suggested the selection of a propionyloxy or butyryloxy group at the C7 position and actually would have led a skilled artisan away from the defined combination of claim 102 and to the selection of an acetoxy group at the C7 position. Thus, the compounds of claim Group VI are patentable in view of the '208 patent.

2. U.S. Patent No. 6,610,860

The compounds of claim 1 of U.S. Patent No. 6,610,860 are mutually exclusive of the compounds of the subject claims. The subject claims do not allow the nitrogen to be substituted with a t-butoxycarbonyl group (see X_5). In contrast, claim 1 of the '860 patent requires the nitrogen be substituted with a t-butoxycarbonyl group. As such, claim 1 of the '860 patent would not have suggested the substitution pattern required by the subject claims. Thus, the subject claims are patentably distinct from claim 1 of the '860 patent.

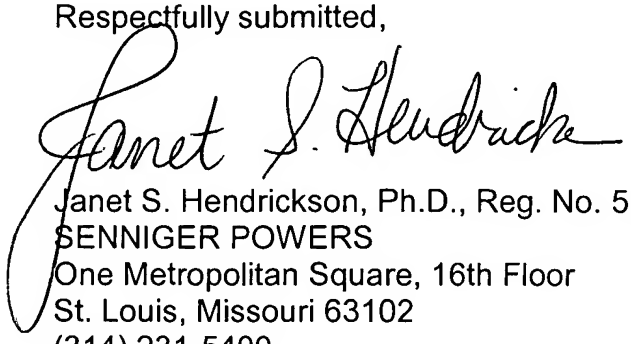
Without conceding the propriety of the rejection, it is noted that the present application claims priority as a continuation of the application which matured into the '860 patent. Accordingly, a terminal disclaimer would not further limit the term of any patent maturing from this application. Applicant's attorney has filed simultaneously herewith a terminal disclaimer with respect to the '860 patent, and thus, the obviousness-type double patenting rejection is traversed with respect to the '860 patent.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

* A check in the amount of $1,650.00 is enclosed ($1,020.00 for a three month extension of time; $500.00 for the Notice of Appeal fee; and $130.00 for the statutory disclaimer). The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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